Acute Exertional Rhabdomyolysis and Its Relationship to Sickle Cell Trait

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ABSTRACT: Exertional rhabdomyolysis, a syndrome characterized by skeletal muscle degeneration and muscle enzyme leakage, has been shown to occur in normal, healthy individuals following strenuous exercise. In severe cases, this syndrome can result in renal failure and sudden death. Although anyone who performs strenuous exercise may be at risk for developing exertional rhabdomyolysis, some individuals may be more susceptible than others. A number of case reports of exertional rhabdomyolysis involve persons with sickle-cell trait, leading to the theory that these individuals might be at greater risk for developing the syndrome than those without this trait. This article discusses the etiology of exertional rhabdomyolysis, the associated risk factors for persons with sickle-cell trait, and the recommended preventive measures. Additionally, several case studies of exertional rhabdomyolysis are reviewed.

Strenuous exercise has been shown to result in leakage of myoglobin and cellular enzymes from skeletal muscle in normal, healthy individuals.[19] In fact, the occurrence of this leakage has been documented in athletes from a variety of sports, including cross-country skiing,[21] marathon running,[24] rowing,[9] soccer,[21] and weight training.[12] However, enzyme leakage resulting from strenuous exercise has also been associated with the potentially life-threatening syndrome known as exertional rhabdomyolysis. In clinical cases of rhabdomyolysis, this release of myoglobin initiates a cycle of metabolic complications, which in severe cases has led to renal failure and death.

Anyone who performs extremely vigorous exercise is at risk for developing this syndrome; poorly conditioned individuals who perform strenuous exercise may be more predisposed.[23] Additionally, numerous case reports[1,6,7,10,11,14,19,23] of exertional rhabdomyolysis have involved persons with sickle-cell trait, leading to the theory that persons with sickle-cell trait might be at greater risk. This article discusses the etiology of exertional rhabdomyolysis and the associated risk factors for persons with sickle-cell trait. Additionally, we will review reported cases and discuss the implications of this syndrome for athletic trainers.

BACKGROUND

The incidence of exertional rhabdomyolysis has been most widely reported and studied in military recruits. The greater occurrence of the syndrome in this population is thought to be due to the extreme physical exertion required during basic training.

As early as 1967, eight cases of exertional rhabdomyolysis and acute renal failure were reported in military recruits.[25] This syndrome gained more attention in 1971, however, when 40 men from a single Marine platoon were hospitalized with symptoms.[3] The increased awareness led to an increase in research efforts to identify the etiology.

Research shows that if muscle cells are damaged due to extreme physical exertion, they release myoglobin and other cellular enzymes into the blood.[8] As blood levels of myoglobin (myoglobinemia) increase, myoglobin eventually spills over into the urine (myoglobinuria) causing the urine to darken in color.[2] Although most cases of rhabdomyolysis result in some degree of myoglobinuria, about 5% to 7% of these cases progress to renal failure.[27] The exact mechanism for this renal failure is unknown. Milne,[15] however, proposes that it is due to renal tubule damage.

In vitro studies show that myoglobin breaks down to globin and ferriheamate with the latter of these two being toxic to renal tubule epithelium.[15] As the renal tubules become damaged, fluid transportation is impaired. This leads to decreased urine excretion and eventual renal failure. Dehydration and/or metabolic acidosis can increase the chance of renal failure.

As exertional rhabdomyolysis progresses, a cascade of electrolyte and enzyme imbalances occur (Table 1). Some of these changes in the blood chemistry have the potential to trigger life-threatening complications. For example, increases in potassium can lead to skeletal muscle weakness as well as abnormal heart contractions and possible cardiac arrest. Similarly, decreased in calcium levels can cause skeletal muscle tremor or tetany and decreased excitability of heart muscle.[2]

Reported cases of exertional rhabdomyolysis follow one of two scenarios: sudden collapse accompanied by acute renal failure or the gradual onset of muscle soreness and renal dysfunction. General signs and symptoms are outlined in Table 2. Severe cases involve sudden collapse, and these symptoms may not be apparent to the athletic trainer.[5,10,19] Therefore, the possibility of exertional rhabdomyolysis should be considered in all athletes, especially those with sickle-cell trait who collapse suddenly after strenuous exercise. With milder cases of exertional rhabdomyolysis, the symptoms are often overlooked initially, since some degree of muscle soreness and

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Table 1. Blood Chemistry Changes Resulting From Exertional Rhabdomyolysis

Electrolyte/Enzyme	Blood level changes
Potassium	Increased
Calcium	Decreased
Phosphate	Increased
Creatine Kinase	Increased
Serum creatinine	Increased
Lactate Dehydrogenase	Increased
Uric Acid	Increased
pH	Decreased

fatigue are expected when beginning a training program or after an excessively strenuous workout. The presence of dark-colored urine is often dismissed initially and thought to be simply the result of increased concentration due to fluid lost through perspiration. Hematuria (gross and/or microscopic blood in the urine) has also been reported to occur in runners due to the repetitive impact forces of footstrike causing damage to red blood cells (hemolysis) or trauma to the bladder.[2] Hematuria, however, is not serious and is usually self-resolving. Myoglobinuria, on the other hand, as described previously, is not self-resolving and, instead, is capable of causing renal failure. Therefore, if darkened urine is reported, particularly when reported in combination with muscle pain or cramping, a physician should be consulted immediately to rule out myoglobinuria and the possibility of exertional rhabdomyolysis.

SICKLE CELL TRAIT AND EXERTIONAL RHABDOMYOLYSIS

In the United States, estimates are that 7% to 9% of the African-American population have the sickle-cell trait. Although rare, sickle-cell trait has also been found in white American individuals who have had ancestral links to Africa, India, or the Mediterranean.[20]

The sickle-cell trait is generally considered a benign condition and therefore should not preclude someone from participating in athletics. In 1973, Murphy[16] studied the prevalence of sickle-cell trait in African-American professional football players. Blood samples were taken from all but nine of the African-American players (n = 579) with 20 of the 26 NFL teams participating in the study. Test results revealed that 39 of these athletes carried the sickle-cell trait. Discussion with the team physicians of these athletes revealed no previous incidence or problem. Therefore, Murphy concluded that sickle-cell trait did not limit the physical capabilities of these athletes. Similarly, Diggs and Flowers[4] screened 142 black high school football and basketball athletes for sickle-cell trait and found 15 athletes (10.5%) who carried this trait. Over a 2-year period, these 15 athletes participated in training programs and two competitive seasons without any evidence of disability or problems. The percentage of sickle-cell trait in these athletic populations was equivalent to that of the general population. Several studies have also shown no difference in the exercise capacity of persons with sickle-cell trait when compared to persons without this trait.[17,18]

Table 2. Signs and Symptoms of Exertional Rhabdomyolysis

1. Muscular weakness
2. Muscular swelling
3. Muscular pain and/or cramping
4. Darkened urine (tea- to cola-colored)

Note: The muscular signs and symptoms are usually confined to the particular overworked muscle group(s).

Despite this research, the fact remains that sickle-cell trait has been associated with episodes of sudden collapse during or immediately after exercise in 30 reported cases with 20 of these cases resulting in death.[5] At least 17 of the total reported cases of sudden collapse and/or death in persons with sickle-cell trait have specifically involved exertional rhabdomyolysis.[1,5,10,11,14,19,23,26,28] Kark[13] retrospectively studied all (n = 62) reported deaths among recruits in basic training from 1977 to 1981 and found that recruits with sickle-cell trait were at a 28 to 40 times greater risk for sudden unexplained exercise-induced death. These sudden unexplained exercise-induced deaths could be related to acute cardiac arrest of undefined mechanism, exertional heat stroke, heat stress, or rhabdomyolysis.

It is not fully understood whether sickle-cell trait itself or some other unidentified but associated metabolic defect makes a small subgroup of patients with sickle-cell trait more susceptible to the development of exertional rhabdomyolysis.[14] Sherry[26] stated that strenuous exercise alone likely does not precipitate the cascade of events leading to exertional rhabdomyolysis in persons with sickle-cell trait. He proposed that dehydration might contribute to the development of sickling in muscle capillaries. As cited by Sherry,[26] Cochran theorized that persons with sickle-cell trait might be naturally more predisposed to dehydration due to their inability to concentrate their urine when deprived of water.[26] This defect might make persons with sickle-cell trait less able to conserve water than persons without this trait. Athletes with sickle-cell trait may require a larger water intake in order to maintain proper fluid balance than those without the trait. This renal concentrating defect in persons with sickle-cell trait could easily exacerbate a state of dehydration caused by viral infection, caffeine or other drug consumption, or excessive perspiration. The primary risk factors for exertional rhabdomyolysis in persons with sickle-cell trait include: 1) extreme heat and humidity, 2) high altitude, 3) exercise-induced asthma, and 4) pre-event fatigue due to illness or lack of sleep.[1]

REVIEW OF SELECT CASE REPORTS

In 1972, a 22-year-old African-American military recruit with sickle-cell trait suddenly collapsed after running 3 miles.[28] Within 4 hours after exercise, he complained of muscle tenderness over the abdomen, back, and extremities. The recruit had experienced diarrhea 2 days before his collapse; however, he had not reported this to medical personnel. Despite immediate treatment for acute renal failure and exertional rhabdomyolysis, the subject died 48 hours later.

Similarly, Koppes[14] described four Air Force recruits with sickle-cell trait who developed exertional rhabdomyolysis

while undergoing training.[14] Three out of the four collapsed suddenly. Two out of the four were described as athletic and had been exercising strenuously for several months; the other two were in good health and had been training for more than 4 weeks. All of the subjects complained of severe muscle cramps and swelling and were diagnosed with exertional rhabdomyolysis associated with acute renal failure. One of the subjects died; the other three survived and recovered normally.

In 1985, two other exercise-related deaths were reported in African-American military recruits with sickle-cell trait.[11,23] Both cases involved sudden collapse after running, the development of exertional rhabdomyolysis with renal failure, and death within 36 hours of the collapse. In 1990, Sherry[26] reported a 17-year-old Air Force cadet with sickle-cell trait who developed exertional rhabdomyolysis and renal failure after performing strenuous calisthenics and a 1.5 mile run. This cadet had been running up to 5 miles a day without difficulty. One week before his collapse, however, he had suffered a viral infection with nausea and vomiting. After regaining consciousness, the cadet complained of severe leg cramps. This cadet eventually recovered.

There have also been several reported cases of exertional rhabdomyolysis involving athletes[1,5–7,10] or recreationally active persons[6] with sickle-cell trait. Helzlsouer et al[10] described an African-American cross-country runner with sickle-cell trait who collapsed suddenly on two separate occasions. After the first incident, the athlete vomited and complained of shortness of breath, abdominal pain, nausea, and leg cramps. He also reported that he had taken a decongestant the evening before his collapse. Although he recovered without complications, he was advised to discontinue competitive running. He continued to run, however, until his second collapse a year later. With the second episode, he required mouth-to-mouth resuscitation and immediate transport to the local emergency room where he was diagnosed with rhabdomyolysis and renal insufficiency. After regaining consciousness, he was disoriented and complained of severe leg cramps. The athlete was discharged from the hospital 1 month later, although he still showed signs of mild renal insufficiency. This athlete no longer runs competitively.

In 1991, a 22-year-old football player suddenly collapsed after completing an 800 m run.[19] This athlete had been training intensively for several weeks and had just passed a preparticipation physical examination. Despite aggressive and immediate treatment for exertional rhabdomyolysis, the patient died 46 hours after his collapse. Autopsy results revealed that the athlete had sickle-cell trait.

Browne and Gillespie[1] reported a case of exertional rhabdomyolysis in a 20-year-old African-American football player with sickle-cell trait. The athlete developed bilateral pain in his lower back, hamstrings, and calves after completing a timed 1-1/2–mile run on the first day of practice. Although the athlete had conditioned over the summer, he had primarily run sprints rather than long distances. The athlete was diagnosed with rhabdomyolysis and exercise-induced asthma and was hospitalized for 4 days. When the athlete's blood chemistries were normal (with the exception of creatine kinase levels, which remained elevated), he was allowed to return to supervised conditioning activities and within 2 weeks returned to full practice with the exception of distance runs. This athlete was "aggressively hydrated" before, during, and after all activity. Due to his exercise-induced asthma, supplemental oxygen was administered during all games. This athlete finished the season without any other episodes of exertional rhabdomyolysis. However, weekly blood tests demonstrated elevated creatine kinase levels throughout the season.

DISCUSSION

Although exertional rhabdomyolysis has not been as widely reported in the athletic population as in the military population, there appears to be a growing number of case reports documenting this syndrome in athletes and/or recreationally active people. For this reason, exertional rhabdomyolysis and its potentially life-threatening sequelae have serious implications for the athletic trainer.

On a daily basis, athletic trainers deal with individuals who perform strenuous exercise. Many of these individuals are at risk for developing exertional rhabdomyolysis due to their sickle-cell trait status, poor level of conditioning, or geographic location (especially hot, humid climates or elevated altitudes). The successful management of this life-threatening syndrome requires early recognition and prompt referral to the nearest emergency room for immediate treatment.

Browne and Gillespie[1] credited their athlete's recovery and return to activity to the fact that both the team physician and athletic training staff were aware of this young man's sickle-cell trait status.[1] This prior knowledge enabled the athletic trainers to quickly recognize the development of this syndrome and therefore seek prompt medical attention. As a result, they recommend that professional and collegiate athletic institutions implement standard sickle-cell trait testing for all athletes at risk, particularly for those athletes whose sports require extreme exertion in either hot, humid climates or locations of high altitude.

Identification of persons with sickle-cell trait, through program-wide testing procedures, could enable athletic trainers, under the direction of their team physician, to implement guidelines for preventing exertional rhabdomyolysis. However, program-wide sickle-cell trait testing is considered controversial by some and unnecessary by others. The cost-effectiveness of such a program has also been questioned since the average cost per sickle-cell trait blood test ranges from $10 to $15. Depending upon an athletic program's size (number of athletes) and budget, this figure could possibly be cost-prohibitive. As suggested by Browne and Gillespie,[1] knowledge of an athlete's sickle-cell trait status can provide an added sense of security when implementing a preventive program for exertional rhabdomyolysis. Additionally, knowledge of an athlete's sickle-cell trait status can facilitate early recognition of this syndrome allowing for prompt treatment and/or referral. Table 3 outlines the recommended measures for preventing exertional rhabdomyolysis in athletes with sickle-cell trait. Many of these measures should be included in any injury/illness prevention plan regardless of sickle-cell trait status.

Athletic trainers who are able to recognize this syndrome and seek prompt medical attention can greatly improve the

Table 3. Recommended Measures for Preventing Exertional Rhabdomyolysis in Athletes With Sickle-Cell Trait

1. Implement a conditioning program prior to athlete's return to sport activity each season.
2. Modify conditioning exercises, as necessary, during the athletic season.[1]
3. Implement aggressive hydration policies before, during, and after all activity.[1,6,15]
4. Educate athletes regarding the dangers of beverages containing caffeine, ie, their diuretic effect.[1]
5. Avoid strenuous exercise in extremely hot and humid conditions.[1,6,15]
6. Avoid strenuous exercise at altitudes above 2500 ft.[1,6]
7. Modify activities after any viral illness, particularly illnesses involving diarrhea or vomiting.[1,6]
8. Modify activities after nights of poor sleep.[1]

outcome for athletes suffering from exertional rhabdomyolysis. It was not our intent to promote or oppose program-wide sickle-cell trait testing. Further investigation is warranted to determine the number of professional and collegiate athletic programs currently testing for sickle-cell trait and the implications of such testing procedures.

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